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EXAMINER	
HAMUD, FOZIA M	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/820,559	PAN ET AL.	
	Examiner	Art Unit	
	Fozia M. Hamud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) *1-4, 15-17,19-21,38-42,53-55 and 57-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *5-14,18,22-37,43-52,56 and 60-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/08/04; 06/15/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restriction:

1a. Applicant's election with traverse of Group II, claims 5-14, 18, 22-37, 43-52, 56, 60-64, (drawn a modified IL-4 mutein receptor antagonist, comprising the amino acid sequence set forth in SEQ ID NO:13), in the reply filed on 13 November 2006, is acknowledged.

Applicants submit that searching and examining the inventions of Groups I and II would not be burdensome, and that as claimed the nucleic acids of Group I cannot encode different polypeptides, but specific polypeptides.

This is considered, but is not found persuasive. Applicants are correct in that as claimed the nucleic acids of Group I cannot encode different polypeptides, but encode specific polypeptides, however, the polypeptides of Group II, which are composed of amino acids and the nucleic acids of Group I, which are composed of purine and pyrimidine units, are structurally distinct molecules. In addition, while a polypeptide of Group II can made by methods using some, but not all, of the nucleic acid that fall within the scope of Group I, it can also be recovered from a natural source using by biochemical means. For instance, the polypeptide can be isolated using affinity chromatography. Contrary to Applicants' argument, searching the inventions of Groups I and II together would impose a serious search burden, because the search of the polypeptides and the nucleic acids are not coextensive, since the sequences are searched in appropriate databases. Finally, the inventions of Groups I and II have a separate status in the art as shown by their different classifications.

Applicants' second ground of traversal is that the office has not conclusively demonstrated why Applicants have to elect a single amino acid sequence, when said amino acid sequences do not have a separate classification, a separate status in the art and/or a different field of search. Applicants contend that the office has only provided reasons why each of the inventions of Groups I-III satisfy MPEP §808.02 A-C, and not reasons for why each of the amino acids as recited in the claims of Group II would satisfy MPEP §808.02 A-C. Thus Applicants submit that at least the polypeptides of SEQ ID NO:13 and 14 should be examined together.

This is considered, but is not found persuasive. The polypeptides of SEQ ID Nos: 10-16, are drawn to muteins of IL-4, wherein amino acids residues at different regions of the IL-4 is modified, for example positions 28, 36, 37, 38, 104, 105 and 106 are modified. However, in the spirit of good customer service, the Examiner has decided to search and examine the polypeptides of SEQ ID Nos: 10-16.

The restriction requirement is still deemed proper and is therefore made FINAL.

Status of Claims:

1b. Original claims 1-64 are pending, of which claims 5-14, 18, 22-37, 43-52, 56, 60-64 will be searched and examined, as they are drawn to the elected invention. Claims 1-4, 15-17, 19-21, 38-42, 53-55, 57-59 are withdrawn from consideration by the Examiner as they are drawn to non-elected invention.

Information Disclosure Statement:

2. The information disclosure statements (IDS) submitted on 08 April 2004 and 15 June 2005 have been received and comply with the provisions of 37 CFR §§1.97 and

1.98. They have been placed in the application file and the information referred to therein has been considered as to the merits.

Claim Objections:

3. Claims 43-56 and 56 are objected to, because they depend from non-elected claims 3 and 41.

Claim Rejections - 35 U.S.C. § 112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4a. Claims 5-14, 18, 31, 32, 33, 34, 35, 43-50, are rejected under 35 U.S.C. 112, first paragraph, while being enabling for a modified IL-4 mutein receptor antagonist comprising the amino acid sequence set forth in SEQ ID NO:12, 13, 14 and 15, wherein said antagonist is coupled to a non-protein polymer at amino acid residue at position 37, 38 or 104 , respectively, wherein said mutein inhibits the stimulation of TF-1 cells induced by IL-4 or IL-13 and wherein said mutein has at least 2-10 fold greater plasma half life than that of an unmodified IL-4 receptor antagonist, is not enabling for 'all possible" modified IL-4 mutein receptor antagonists as recited in claims 5-12, or modified IL-4 mutein receptor antagonists having the amino acid sequence set froth in SEQ ID NO:10, 11, 15 or 16, wherein said muteins inhibit the stimulation of TF-1 cells induced by IL-4 or IL-13, or any IL-4 mutein that inhibits B cell or T cell proliferation. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, how to make or use the invention commensurate in scope with these claims.

Claims 5-12 encompass "all possible" modified IL-4 muteins that bind to IL-4 receptor and that inhibit IL-4 and IL-13 mediated activities, however, the instant specification discloses only modified IL-4 receptor modified at positions 28, 36, 37, 38, 104, 105 and 106, (comprising SEQ ID Nos: 10-16, respectively), of IL-4R antagonist, wherein the amino acids at said positions were substituted with cysteine, and pegylated forms of said polypeptides, (see tables 2 and 7, on pages 20 and 46, respectively). The specification further discloses that only pegylated, modified IL-4 muteins that comprise SEQ ID NO:12, 13 and 14, wherein residues at positions, 37, 38 and 104 of IL-4R antagonist have been substituted with cysteine, bind to IL-4 receptor and inhibit TF-1 cells at IC_{50} comparable to that of IL-4RA in the presence of IL-4 or IL-13, (see Example 5, on page 46 and table 6 on pages 46-47). Therefore, although the instant specification discloses modified IL-4 muteins that are modified at positions 28, 36, 105 and 106 of IL-4R antagonist, (SEQ ID Nos: 10, 11, 15 and 16, respectively), the specification does not teach that said muteins inhibit IL-4 and IL-13 mediated activities. Furthermore, the specification does not disclose that any of the disclosed modified IL-4 muteins inhibit the proliferation of human B cells or human T cells as recited in claims 10, 11, 33 and 34, (see example 6 and table 7). With respect to claims 18, 37 and 56, while the instant specification is enabling for a modified IL-4 mutein receptor antagonist comprising the amino acid sequence set forth in SEQ ID NO:12, 13 or 14, wherein said antagonist is coupled to a non-protein polymer at amino acid residue at position 37, 38

or 104 , respectively, and demonstrates that said muteins inhibit IL-4 and IL-13 mediated TF-1 cells proliferation, it does not disclose a pharmaceutical composition comprising modified IL-4 mutein receptor antagonists. For claims 18, 37 and 56 to be enabled, the specification must teach how to use the composition for at least one pharmaceutical use without undue experimentation. In the present situation, to enable a pharmaceutical use for modified IL-4 mutein receptor antagonists requires the specification to teach how to use the substance, without undue experimentation, for the prevention, diagnosis, alleviation, treatment or cure of a disease in the animal to which the substance is administered. It is recognized in the relevant art that IL-4 and/or IL-13 play a role certain diseases, such as allergic responses and that expression of IL-4 and IL-13 mRNA are increased in asthmatic airways, (see Kips et al, European Respiratory Journal, Vol. 17, pages 499-506, 2001). Kips et al state that, although antagonizing IL-4 and IL-13 may have therapeutic potential in certain diseases, care must be taken not to influence Th1/Th2 balance in favor of Th1 over-stimulation, (see page 501, paragraph 2). In the instant case, the specification does not provide adequate guidance as to how modified IL-4 mutein receptor antagonists can be used to treat diseases that involve IL-4/IL-13. Thus, one of ordinary skill in the art would not know how to use a pharmaceutical composition comprising modified IL-4 mutein receptor antagonists.

To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner, especially given the fact that the specification teaches that not all of the disclosed

modified IL-4 muteins display the desired activity. It is this additional characterization of the disclosed protein that is required in order to obtain the functional and structural data needed to permit one to produce a polypeptide which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation. The criteria set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims, is the basis for determining undue extermination. In the instant case, Due to the large quantity of experimentation necessary to generate the infinite number of modified IL-4 muteins recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which residues tolerate alterations, where to add additional amino acid residues, in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. Accordingly, the instant specification is only enabling for modified IL-4 mutein receptor antagonist comprising the amino acid sequence set forth in SEQ ID NO:12, 13 or 14, wherein said antagonist

is coupled to a non-protein polymer at amino acid residue at position 37, 38 or 104 , respectively.

Priority

5. Applicant's claim for priority under 35 U.S.C. 119(e) U.S. Provisional Application No: 60/498,906, (29 August 2003) is acknowledged. Thus the effective fling date of 29 August 2003 is used for the purposes of applying prior art.

Claim Rejections - 35 USC § 102:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6a. Claims 5, 6, 12, 13, 22, 26, 28, 30, 60, 62-64 and 43-44, 50-52, are rejected under 35 U.S.C. 102(b) as being anticipated by Wild et al U.S. Patent 6,130,318, 10 October 2000.

Wild et al disclose several human IL-4 mutant proteins in which specific amino acids residues are modified, for example where residues at position 38 and 105 are modified, (page abstract and column 3, lines 35-50). Wild et al also disclose modification of IL-4 by linking it to non-protein polymers, such as polyethelyne glycol, polypropylene glycol or polyoxyalkylenes to improve the half-life of the protein, (see column 7, lines 19-37). Wild et al also disclose the IL-4 mutants they disclose inhibit IL-4 mediated processes and act as IL-4 antagonists, (see column 8, lines 15-20). Wild et al teach that conjugating IL-4 to a polymer prolongs circulating half life of the protein.

Also taught are recombinant materials for making such a fusion protein, vectors and expression; see examples 1-4.

The instant claims 5, 6, 7, 12, 13, 22, 26, 28, 30, 35, 60, 62-64 and 43-44, 50-52, encompass modified IL-4 mutein receptor antagonists, which bind to the IL-4 receptor, or that are coupled to non-protein polymers, such as polyethylene glycol, polypropylene glycol or polyoxyalkylenes, or muteins produced by processing a host cell comprising polynucleotide which encodes for the polypeptide of SEQ IDD NO:13 or 15, said muteins which are modified at positions 38 or 105.

Therefore, the U.S. Patent 6,130,318, meets all the limitations recited in instant claims 5, 6, 12, 13, 22, 26, 28, 60, 62-64, 43-44, 50-52, thus anticipating theses claims in the absence of any evidence on the contrary.

Claim Rejections - 35 USC § 103:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7a. Claims 5-7, 14, 7, 22-30, 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wild et al U.S. Patent 6,130,318, 10 October 2000 in view of Kreitman et al (1994).

The teachings of Wild et al are discussed directly above. However, Wild et al do not teach modified IL4 mutein, wherein specific amino acid residues are substituted with a cysteine residue in order to conjugate said mutein to another molecule.

Kreitman et al disclose several human IL-4 mutant proteins in which specific amino acids residues are modified, where residues at position 28, 38, or 105 have been substituted with a cysteine, wherein said mutein is attached to a toxin and wherein said fusion protein binds to IL-4 receptor, (abstract and page 11643, column 1).

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the polypeptide of Wild et al to substitute desired amino acid residues with cysteine residues as taught by Kreitman et al. The person of ordinary skill in the art would have been motivated to make the modification in view of Kreitman et al disclosure that site specific conjugation by cysteine mutagensis of IL-4 is a feasible way to study the potential role of IL-4 and IL-4 receptor in disorders. Accordingly, the invention, taken as a whole, is prima facie obvious over the cited prior art.

Conclusion:

8. No claim is allowed.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia M. Hamud whose telephone number is (571) 272-

0884. The examiner can normally be reached on Monday, Thursday-Friday, 6:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Fozia Hamud
Patent Examiner
Art Unit 1647
13 December 2006

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